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EXAMINER	
ROOKE, AGNES BEATA	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,194	UMEZAWA ET AL.	
	Examiner	Art Unit	
	Agnes B. Rooke	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *8-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *Jan 26, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response the paper filed on 08/09/2007. The Applicants elected Group I, claims 1-7, without traverse.

Claims 8-14 are withdrawn from further consideration pursuant to 37 CFR 1.12(b), as being drawn to a non-elected invention.

A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP paragraph 821.01. Therefore, the restriction is Final.

Status of Claims

2. Claims 1-14 are pending. Claims 1-7 are elected and under consideration. Claims 8-14 are withdrawn.

Priority

3. This application is a 371 of PCT/JP04/03433 filed on 03/15/2004 that claims foreign priority to JAPAN 2003-120253 filed on 04/24/2003.

Drawings

4. Drawings submitted on 10/24/2005 are accepted by the examiner.

IDS

5. The Information Disclosure Statements filed on 10/24/2005 have been received and entered. The references cited on the PTO-1449 Form have been considered by the examiner and copy is attached to the instant Office Action.

Objection to Claims

6. Claim 3 is objected to for clarity purposes because the name "GRP1" should be fully spelled out at the first instance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claim is directed to a probe that comprises a polypeptide that can bind the lipid second messenger, two chromophores wherein each chromophore is linked to each end of the polypeptide through linker sequence and a membrane localization sequence that binds to one of the chromophores. In the instant claims 1 and 2, there is no indication of the structure of eth protein being claimed and thus the function of eth protein does not correspond to its function. Further, a membrane localization sequence is not disclosed, thus the structure of eth sequence does not correspond to its function. Further, there is no recitation of the source of the protein(s) or the identity of the specific protein being claimed.

In addition, in claim 3, the pleckstrin homology domain from GRP1 represents a very broad genus of sequences because the term homology

represents only similarity between characters that perform the same function in different biological species and the term does not mean an identity to a specific sequence. Thus, different homologs are unknown and undisclosed, and the structure of the homologs do not correspond with their function.

Additionally, the instant specification does not provide a representative number of species for the claimed genus of probes that comprise different protein structures that bind to a lipid second messenger, for example.

A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

The claimed genus of pleckstrin homology domain from GRP1 is not disclosed or specifically discussed. Therefore, the homology domains represent many variables and the detailed structure of pleckstrin homology domain cannot be envisioned or specifically determined.

Therefore, the genus of claimed polypeptides encompasses widely variant species. As such, neither the description of the structure and function of the pleckstrin homology domains is sufficient to be representative of the attributes and features of the entire genus. Based on the unlimited variations contemplated one skilled in the art would at best expect a protein that is different or at worst a protein that is not functional.

Claim 5 is included in this rejection because even though a specific structure of the link is disclosed as SEQ ID NO:1, the instant claim 1 is very broad and claim 5 does not correct the deficiency of claim 1, since claim 1 does not provide any structure for the linker and thus the structure of the probe does not correspond with its function.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The

compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

8. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the a probe where the lipid second messenger-binding protein is the pleckstrin domain from GRP1 and where the linker sequence is SEQ ID NO:1 and where at least one linker sequence has a single di-glycine motif, the specification does not reasonably provide enablement for a probe with any polypeptide that bind any lipid second messenger and that contains any membrane localization sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue.

These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified polypeptides that bind the lipid second messenger and it is not certain which polypeptides would work adequately in a probe and whether any pleckstrin homology domain would have the same function as the pleckstrin from GRP1. The instant specification does not demonstrate or provide guidance as to what the structure of the protein will be once modified or if said protein will be functional or exhibit the same properties or characteristics as the native protein. Additionally, there is no data provided demonstrative of a particular portion of the structure that must be conserved, for example what amino acids are for the pleckstrin homology domain structure to retain the function since there are many variants of such a peptide possible. Therefore, the claims encompass variants or fragments that may not have any biological activity. Due to the large quantity of experimentation necessary to generate the infinite number of variants/fragments recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation.

Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. In the instant case, there are no working examples that will refer different proteins that are different than pleckstrin domain from GRP1 and would have the same effect and function in the probe as claimed. Further, it is not certain whether any membrane localization sequence will have the same effect in the probe as claimed. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial

orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims.

The state of the prior art provides evidence for the pleckstrin domain of GRP1 but does not disclose all possible homology domains of the pleckstrin, since unpredictable cleavage sites can be formed with variable amino acids placed in those cleavage sites that would no longer retain the desired function.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure. In the instant case there is no guidance in regards to any protein that binds the lipid second messenger (claim 1) or any pleckstrin homology domain from GRP1 (claim 3) or any possible transmembrane sequence (claim 7), for example.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variant. The nature and

properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct the variants of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of variants/fragments and a plurality of amino acids that can compose a polypeptide, which can specifically bind the lipid second messenger.

The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*. Therefore, absent direction/guidance regarding whether the structure of a polypeptide that can bind the lipid second messenger can tolerate the modifications contemplated a non-functional protein may result and one of skill in the art would not be able to practice the claimed invention commensurate in scope with the claims. In addition, absent direction/guidance regarding the specific polypeptides that bind

the lipid second messenger, one of skill in the art would not be able to make the claimed probe and still retain the desired function.

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible variants of a polypeptide that binds the second messenger, and then to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. Claims 1-4, 6, and 7 are rejected under 35 U.S.C. 102(e) as being anticipated by Jalink (U.S. 6,596,499, December 2000).

Jalink teaches PIP2 indicator (which is a lipid second messenger) that contains a first polypeptide having a pleckstrin homology domain and a donor fluorescent domain and a second polypeptide with an acceptor fluorescent domain, see column 2, lines 10; where in column 6, lines 1-9, Jalink teaches membrane molecule indicator compositions that contain peptide or non-peptide domains, such as linker sequences between the donor fluorescent domain and acceptor fluorescent domain, or between a fluorescent domain and either the membrane molecule indicator domain or the membrane anchor, where as depicted by Figures 9 and 10, fluorescent domains can optionally contain membrane anchor domains. (instant claims 1-3 and 7 where the membrane localization sequence is a tarnsmembrane sequence).

The fluorescent domains that can be used in the composition are green fluorescent protein (GFP) see column 13, lines 6-7; or cyan fluorescent proteins (CFP) see column 13, lines 45-46. (instant claim 4).

The linker moiety has Gly-Gly (instant claim 6 where the linker sequence has a single di-glycine motif).

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnes Rooke whose telephone number is

571-272-2055. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.

AR

HOPE ROBINSON
PRIMARY EXAMINER
10/29/07